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Case report

# Treatment of acute erythroleukemia with Azacitidine: A case series

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ABSTRACT

Acute erythroleukemia (AEL) is a rare form of acute myeloid leukemia (AML) often associated with a poor prognosis. It is more frequent in elderly patients, limiting the use aggressive therapies. Azacitidine is a hypomethylating agent with recognized efficacy in high risk myelodysplasia and AML in the elderly. Here we report 5 cases of AEL treated with Azacitidine. The cohort included 4 men and 1 woman, median age 70. One patient had been refractory to intensive chemotherapy, the others received Azacitidine as first line. Treatment was well tolerated. Four patients achieved transfusion independence. Two patients achieved complete remission and 1 achieved partial remission. After a median follow up time of 20 months, the median survival of the cohort was 20 months. Three patients died of disease progression. These results confirm the therapeutic value of Azacitidine in AEL.



## 1. Introduction

Acute erythroleukemia (AEL) is a rare subtype of acute myeloid leukemia (AML), accounting for 3–5% of all AML cases[1]. It is characterized by the expansion of erythroblasts in the bone marrow (BM)[2,3]. Its clinical presentation often resembles myelodysplastic syndromes (MDS), both in terms of indolent cytopenias[2] and older median age at diagnosis of 65[4]. High risk karyotypes, with hypodiploidy, complex alterations (including abnormalities of chromosomes 5 and 7) and monosomies are frequent[1]. Consequently, AEL is associated with poor prognosis, with a median survival of 3–9 months from diagnosis[4].

It is traditionally treated with intensive chemotherapy, achieving rates of complete remission (CR) of approximately 55% but these last less than a year[1]. As in other AML subtypes, patients with high risk cytogenetics should be considered for allogeneic bone marrow transplant[1]. However, the fact that most patients are elderly and frail means that aggressive treatment options are often not possible, limiting management to supportive care.

In the last few years hypomethylating agents have become the first line therapy for patients with MDS and AML who are not candidates for aggressive chemotherapy, including bone marrow transplantation[5]. Azacitidine has demonstrated to grant patients with high risk MDS and AML with 20–30% blasts a survival advantage compared to conventional care regimens[6].

There are several reports of use of Azacitidine in AEL, including a series of 17 patients, where CR was achieved in 58%, median disease free survival of 11 months and median survival of 12 months[7].

Here we report a case series of five patients with AEL diagnosed at our institution and treated with Azacitidine (AZA).

Although the standard AZA administration schedule is 75 mg/m$^2$/day for 7 days every 28 days (75 × 7), at our institution, due to lack of availability of weekend administration and patient travel constraints, we adopted an alternate dose-intensified schedule over a shorter period of time (500 mg/m$^2$ total monthly dose divided in 5 days) with daily dose adjustment in order to avoid weekend administration and vial wastage. Using this regimen in high risk MDS patients we have observed similar efficacy and safety profiles as those published with the 75 × 7 schedule.

### 1.1. Patient population

Between 2009 and 2012, 6 patients with AEL classified according to WHO 2008 criteria were diagnosed at our institution. Five patients were treated with AZA. The median age at presentation was 70 and most patients were men. All patients presented with transfusion dependent anemia, requiring a median of 3 units packed red blood cells per month. Poor risk karyotype was found in 3 patients.

The presentation features are detailed in Table 1.

All patients apart from patient 1 received Azacitidine as first line therapy. Patient 1 received one course of intensive chemotherapy, to which the disease was refractory, prior to starting Azacitidine.

Azacitidine was administered subcutaneously as a five-day regimen (500 mg/m$^2$ total dose divided in 5 administrations) with daily dose adjustment to the nearest 100 mg repeated every 4 weeks. Patients received supportive care at the physician's discretion. Marrow response was assessed following the 6th treatment cycle.

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Responses were classified according to the modified IWG criteria[8]. Marrow remission was documented in 2 patients and partial remission in one patient. Three patients achieved transfusion independence after a median of 4 cycles. Table 2 details the responses achieved with Azacitidine.

All patients were treated until disease progression apart from patient 1, who received an unrelated bone marrow transplant at the end of 16 cycles of Azacitidine. A mean of 10 cycles (1–17) of Azacitidine were administered per patient.

Treatment with Azacitidine was well tolerated. Grade 1/2 toxicities, seen in all patients, were local injection site erythema, constipation, neutropenia and thrombocytopenia, the latter seen mostly in the first 4 cycles. There were no admissions to hospital during the treatment period and there were no treatment suspensions due to adverse events.

In this small cohort with a median follow up time of 25.9 months the median survival from diagnosis was 26 months. If the patient who underwent transplant is censored, the median survival was 22 months. At the time of data collection, three patients had died, all of disease progression.

## 2. Discussion

AEL is a rare subtype of AML commonly associated with previous myelodysplasia, complex karyotype and poor prognosis. Conventional treatment options are often limited, raising the need for novel approaches. Azacitidine, licensed for use in high risk MDS, has demonstrated efficacy in a small series of AEL patients[7].

Here we presented the results of Azacitidine in five patients diagnosed with AEL.

Our report differs from the only other published report of hypomethylating agents in erythroleukemia[7] in several aspects. Our patient group is more uniform: all patients were treated with AZA as monotherapy compared to 35% who were treated with decitabine and 30% who received concomitant histone deacetylase inhibitors. The proportion receiving AZA as second line therapy was similar to that previously published[7]. The response rate was similar but treatment duration and overall survival in our cohort were longer: 10 cycles compared to 5 cycles and median survival of 22 months compared to 12 months.

Treatment was administered on an outpatient basis, for 5 days every 28 days, providing a good quality of life for the patients. Therapy was well tolerated, with minimal toxicity. None of the patients required admission for febrile neutropenia and or drug interruption for grade 3–4 toxicities.

Transfusion independence was achieved in all the patients. Two patients achieved marrow remission and one achieved a partial remission, all of which lasted over 18 months.

The favorable results obtained with the 5-day schedule raise the question of whether patients with AEL respond better to a dose intensified regimen. This would need to be verified in a larger cohort, preferably in the context of a trial.

In patient 1, who had been refractory to intensive chemotherapy, Azacitidine permitted disease control for over 1 year during the search for a compatible bone marrow donor and preparation for SCT. Reduced intensity conditioning regimens have opened the option of SCT to more elderly and frail patients but the toxicities associated with conventional intensive AML induction chemotherapy can increase the risk of death or compromise SCT. It has been shown recently that Azacitidine before SCT does not significantly affect rates of remission, relapse, acute and chronic GVHD and

**Table 1**
Patient characteristics at presentation.

| | Age | Gender | Hb (g/dL) | Neutrophils ($\times 10^9$/L) | Platelets ($\times 10^9$/L) | Percentage of marrow blasts** | Karyotype | Comorbidities |
|---|---|---|---|---|---|---|---|---|
| 1* | 62 | Male | 8.0 | 0.4 | 60 | 36 | 46,XY,del(5)(q15q?31)[5]/46,XY[20] | Obesity, cholecytitis, BPH |
| 2 | 65 | Male | 7.7 | 1.3 | 673 | 17.5 | 46XY[20] | Ischemic heart disease |
| 3 | 73 | Female | 8.0 | 1.0 | 113 | 33 | 48,XX,+1, del(5)(q13q33∼34) or del (5)(q15q35),+11, +18,-22[8]/48, idem,add(21)(p1?3)[2]/46,XX[2] | None |
| 4 | 70 | Male | 9.5 | 1.1 | 30 | 25 | 46,XY,del(5)(q13q33 or q15q35)[10]/ 46,XY[14] | None |
| 5 | 76 | Male | 6.8 | 0.2 | 124 | 40 | 46,XY,del(5)(q1?4q3?3)[15]/46,XY, −7,+mar[1] | DM type II |

Hb: hemoglobin; BPH: benign prostatic hypertrophy; DM: diabetes mellitus.

* Patient 1 received prior intensive chemotherapy.

** Calculated in non-erythroid component.

**Table 2**
Responses with Azacitidine.

| | Cycles AZA received | Best hematological response | Time to first response (cycles) | Marrow response at 6th cycle | Survival (months from start of therapy) | Survival (months from diagnosis) |
|---|---|---|---|---|---|---|
| 1* | 16 | Transfusion independence | 4 (TI) | Marrow CR | 28+ | 29+ |
| 2 | 17 | Transfusion independence | 5 (TI) | CR | 19 | 20 |
| 3 | 9 | No response | 6 (marrow PR) | PR | 24+ | 25+ |
| 4 | 1 | No response | – | Not applicable | 2 | 4 |
| 5 | 9 | Transfusion independence | 4 (TI) | Stable | 16 | 24 |

AZA: Azacitidine; CR: complete remission; PR: partial remission; TI: transfusion independence.

* Patient 1 received prior intensive chemotherapy.

survival after transplant and may actually be an alternative for inducing remission in patients with high risk MDS and eventually AEL[9].

The results from this cohort confirm the therapeutic value of Azacitidine in AEL, with improvement in TI, maintenance of autonomous daily activities and permitting a curative approach in those who are transplant candidates. Large, prospective clinical trials are needed to confirm these results and to establish the use of hypomethylating agents in AEL.

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## References

1. Santos FP, Bueso-Ramos CE, Ravandi F. Acute erythroleukemia: diagnosis and management. *Expert Review of Hematology* 2010;**3**(6)705–18.
2. Hasserjian RP, Zuo Z, Garcia C, Tang G, Kasyan A, Luthra R, et al. Acute erythroid leukemia: a reassessment using criteria refined in the 2008 WHO classification. *Blood* 2010;**115**(10)1985–92.
3. Liu W, Hasserjian RP, Hu Y, Zhang L, Miranda RN, Medeiros LJ, et al. Pure erythroid leukemia: a reassessment of the entity using the 2008 World Health Organization classification. *Modern Pathology* 2011;**24**(3)375–83 Mar.
4. Santos FP, Faderl S, Garcia-Manero G, Koller C, Beran M, O'Brien S, et al. Adult acute erythroleukemia: an analysis of 91 patients treated at a single institution. *Leukemia* 2009;**23**(12)2275–80.
5. Santini V, Alessandrino PE, Angelucci E, Barosi G, Billio A, Di MM, et al. Clinical management of myelodysplastic syndromes: update of SIE, SIES, GITMO practice guidelines. *Leukemia Research* 2010;**34**(12)1576–88.
6. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncology* 2009;**10**(3)223–32.
7. Vigil C, Cortes J, Kantarjian H, Garcia-Manero G, List AF. Hypomethylating therapy for the treatment of acute erythroleukemia patients. *Blood* 2009:1–12.
8. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006;**108**(2) 419–425.
9. Field T, Perkins J, Huang Y, Kharfan-Dabaja MA, Alsina M, Ayala E, et al. 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 2010;**45**(2)255–60.